CLAIMS

1. Implant characterized in that it comprises :

- a biocompatible support permitting the biological anchoring of cells,
- cells having the capacity to express and secrete naturally or after recombination a defined substance, for example a substance having therapeutic value; and
- a constituent capable of inducing and/or promoting the gelation of said cells.

2. Implant according to Claim 1, characterized in that the biocompatible support includes at least one of the elements selected from the group comprising PTFE or a support of biological origin.

3. Implant according to Claim 1, characterized in that the biocompatible support is a support of biological origin of the type resorbable <u>in vivo</u>, at least partially.

4. Implant according to any one of the Claims 1 to 3, characterized in that the biocompatible support is a calcium-based, in particular a calcium carbonate- based, support, preferably it is coral.

5. Implant according to Claim 4, characterized in that the biocompatible support is high-porosity coral.

6. Implant according to Claim 3 or Claim 5, characterized in that the high-porosity coral is a spherical coral.

7. Implant according to any one of the Claims 1 to 6, characterized in that the constituent capable of inducing and/or promoting the gelation of the cells is collagen, in particular type I collagen, preferably at a concentration of the order of 1.5 mg/ml.

8. Implant according to Claim 1 or Claim 3, characterized in that the biocompatible support is selected from :

- cross-linked collagen, in particular in the form of fibers or sponges,
- bone powder,
- carbohydrate-based polymers such as dextran or hyaluronic acid.

9. Implant according to any one of the Claims 1 to 8, characterized in that the constituent capable of inducing and/or promoting the gelation of the cells is selected from supports based on :

- uncross-linked collagen,

- alginates.

10. Implant according to any one of the Claims 1 to 9, characterized in that the cells are recombinant cells having the capacity to be tolerated immunologically by an organism to which they are administered, modified by a nucleotide sequence coding for a defined polypeptide.

11. Implant according to Claim 10, characterized in that the recombinant cells are fibroblasts, in particular skin fibroblasts.

12. Implant according to any one of the Claims 1 to 11, characterized in that said cells are recombinant cells modified by a retroviral vector comprising a proviral DNA sequence modified in a manner such that :

- the gag, pol and env genes of the proviral DNA have been deleted at least in part in order to produce a proviral DNA incapable of replicating, this DNA being in addition incapable of recombining to form a wild-type virus,

- the LTR sequence contains a deletion in the sequence U3 such that transcription of the mRNA that it controls is reduced significantly for example at least 10-fold, and the recombinant retroviral vector comprises, in addition, an exogenous nucleotide sequence under the control of a promoter for example an exogenous, constitutive or inducible promoter.

13. Implant according to Claim 12, characterized in that the proviral DNA of the vector is derived from the MuLV retrovirus.

14. Implant according to Claim 11 or Claim 12, characterized in that the sequences of the pol and env genes of the proviral DNA are entirely deleted.

15. Implant according to any one of the Claims 11 to 13, characterized in that the U3 region of the LTR3' fragment of the proviral DNA is deletedat the level of nucleotide 2797 of Figure 1.

16. Implant according to any one of the Claims 12 to 15, characterized in that the exogenous nucleotide sequence is under the control of the mouse PGK-1 promoter or the human PGK-1 promoter, optionally lacking a "TATA box".

17. Implant according to any one of the Claims 12 to 16, characterized in that the proviral sequence upstream from the exogenous promoter is the proviral nucleotide sequence situated

between nucleotides 1 and about 1500 of the sequence shown in Figure 1.

18. Implant according to any one of the Claims 12 to 17, characterized in that the retroviral vector is the vector pM48 shown in Figure 2, modified by the insertion of the exogenous nucleotide sequence at the BamHI site.

19. Implant according to any one of the Claims 1 to 10 or 12 to 18, characterized in that the recombinant cells are tumor cells.

20. Implant according to any one of the Claims 1 to 19, characterized in that the recombinant cells are modified by a vector containing one or more exogenous nucleotide sequences coding for an antigen or an antigenic determinant or coding for a polypeptide or glycoprotein soluble in the serum, for example a polypeptide or a glycoprotein of therapeutic interest, in particular a hormone, a structural protein or glycoprotein or a metabolic protein or glycoprotein or a viral protein or glycoprotein or a protein having the characteristics of an antibody or an antibody fragment.

21. Implant according to any one of the Claims 1 to 20, characterized in that it contains in addition one or more angiogenic factors, in particular bFGF.

22. Implant according to any one of the Claims 1 to 21, characterized in that it contains heparin or a heparin derivative.

23. Implant according to any one of the Claims 1 to 22, characterized in that it contains from 10^6 to 10^9, and preferably from 5×10^6 to 10^7 recombinant cells.

24. Use of an implant according to any one of the Claims 1 to 23, in a permanent or temporary fashion, for the implantation in man or animals.

25. Use of an implant according to any one of the Claims 1 to 23 :

- either for the treatment of genetic diseases, in particular for the treatment of diseases of lysosomal overload, hemophilia A or hemophilia B, beta-thalassemia, the exogenous nucleotide sequence contained in the recombinant cells corresponding respectively to those which code for beta-glucuronidase, for the factor VIII, factor IX or erythropoietin, or for an active part of these sequences;

- or for the treatment of acquired diseases, for example for the treatment of viral diseases, in particular for the treatment of an infection due to the HIV retrovirus, for example by the expression

and secretion into the serum of soluble CD4 molecules or a soluble anti-viral protein;

- or for the treatment of tumors, the exogenous nucleotide sequence contained in the recombinant cells coding for a substance capable of promoting or enhancing the immune response against the cells of the tumors.

26. Composition characterized in that it contains an implant according to any one of the Claims 1 to 23 with one or more substances, in particular an antigen or an adjuvant.

27. Method of treatment of genetic diseases, acquired diseases or tumors, said method comprising the introduction into man or animals of an implant according to any one of the Claims 1 to 23 for a period of time sufficiently long to allow the cells included in said implant to produce in vivo a peptide, a protein or a glycoprotein having a therapeutic effect on the disease to be treated.

28. Method according to Claim 7, characterized in that said implant is introduced in the peritoneal cavity, the peri-renal space or the skin of the patient to be treated.

29. Method of preparation of an implant according to any one of the Claims 1 to 23, said method comprising the steps of :

- placing of the biocompatible support in contact with said cells and a constituent capable of inducing and/or promoting their gelation;

- incubation of the preparation obtained in the previous step in order to obtain the gelation of said constituents;

- culture of the cells thus obtained under conditions allowing them to bind to the gelled constituents, and

- recovery of the implant thus obtained.

30. Method according to Claim 29, characterized in that the biocompatible support is placed in contact with cells previously incorporated into a solution of collagen.

31. Method according to Claim 29 or 30, characterized in that the biocompatible support is constituted of PTFE fibers or coral powder, previously treated with a solution of collagen or a growth factor.

32. Recombinant retroviral vector characterized in that it comprises :

° a proviral DNA sequence modified in a manner such that :

- the gag, pol and env genes of the proviral DNA have been deleted at least in part in order to produce a proviral DNA incapable of replication, this DNA being in addition unable to recombine for form a wild-type virus,

- the LTR sequence bears a deletion in the U3 sequence such that transcription of mRNA that it controls is reduced significantly, for example by at least 10 fold, and

° the recombinant retroviral vector comprising in addition an exogenous nucleotide sequence under the control of a promoter for example an exogenous, inducible or constitutive promoter.

33. Retroviral vector according to Claim 32, characterized in that the modified proviral DNA sequence, the exogenous nucleotide sequence and the exogenous promoter are borne by a plasmid.

34. Retroviral vector according to Claim 1 or Claim 33, characterized in that the proviral DNA is derived from the MuLV retrovirus.

35. Retroviral vector according to any one of the Claims 32 to 34, characterized in that the sequences for the pol and env genes of the proviral DNA are entirely deleted.

36. Retroviral vector according to any one of the Claims 32 to 35, characterized in that the U3 region of the LTR3'fragment is deleted at the level of nucleotide 2797 of Figure 1.

37. Retroviral vector according to any one of the Claims 32 to 36, characterized in that the exogenous nucleotide sequence is under the control of the mouse PGK-1 promoter or the human PGK-1 promoter, optionally lacking a "TATA box".

38. Retroviral vector according to any one of the Claims 32 to 36, characterized in that the proviral sequence upstream from the exogenous promoter is the proviral nucleotide sequence situated between the nucleotides 1 and about 1500 of the sequence shown in Figure 1.

39. Retroviral vector according to Claim 37, characterized in that the exogenous nucleotide sequence is inserted at the BamHI site downstream from the exogenous constitutive PGK-1 promoter

40. Retroviral vector according to any one of the Claims 32 and 39, characterized in that it is the pM48 vector shown in Figure 2, modified by the insertion of the exogenous nucleotide sequence at the BamHI site

41. Retroviral vector according to any one of the Claims 32 to 40, characterized in that it contains at the BamHI site downstream from the exogenous constitutive promoter a BamHI fragment of the gene of beta-galactosidase.

42. Retroviral vector according to any one of the Claim 32 to 41, characterized in that it contains in addition upstream from the exogenous constitutive promoter an enhancer sequence.

43. Recombinant cells characterized in that they are cells having the capacity to be tolerated immunologically by the organism to which they are administered, modified by a retroviral vector according to any one of the Claims 32 to 42.

44. Recombinant cells according to Claim 43, characterized in that they are recombinant fibroblasts, in particular skin fibroblasts.

45. Recombinant cells according to Claim 43, characterized in that they are tumor cells modified by a retroviral vector according to any one of the Claims 32 to 42.

46. Recombinant cells according to any one of the Claims 43 to 45, characterized in that the exogenous nucleotide sequence which they contain codes for a protein whose expresion is desired, in particular a protein soluble in the serum.

47. Recombinant cells according to any one of the Claims 43 to 46, characterized in that the exogenous nucleotide sequence which they contain codes for beta-glucuronidase.

48. Use of the recombinant cells according to any one of the Claims 43 to 47 for the treatment of a disease capable of being corrected by the expression and secretion into the serum of a patient of the exogenous nucleotide sequence contained in these cells.

49. Use of the recombinant cells according to any one of the Claims 43 to 47 for the treatment of genetic diseases, in particular for the treatment of diseases of lysosomal overload, hemophilia A or hemophilia B, beta-thalassemia, the exogenous nucleotide sequence contained in the recombinant cells corresponding respectively to those which code for beta-glucuronidase for the factor VIII, factor IX or erythropoietin or for an active part of these sequences.

50. Use of the recombinant cells according to any one of the Claims 43 to 47 for the treatment of acquired diseases, for example for the treatment of viral diseases, in particular for the treatment of an infection due to the HIV retrovirus for example by the expression

and secretion into the serum of soluble CD4 molecules or of a soluble anti-viral protein.

51. Use of the recombinant cells according to any one of the Claims 43 to 47 for the preparation of antibodies against the expression product of the exogenous nucleotide sequence contained in the recombinant cells.

52. Use of the recombinant cells according to any one of the Claims 43 to 47 for the treatment of tumors, the exogenous nucleotide sequence contained in the recombinant cells coding for a substance capable of promoting or enhancing the immune response against the cells of the tumor.

53. Recombinant cells according to Claim 52 such as obtained by recombination of tumor cells with a retroviral vector according to any one of the Claims 32 to 42.

54. Kit for the preparation of an implant to achieve the in vivo expression and secretion by cells of a substance to produce a desired therapeutic effect, said kit containing :

- a biocompatible support making possible the biological anchoring of said cells, and
- a constituent capable of inducing and/or promoting the gelation of said cells.

55. Kit according to claim 54, characterized in that the biocompatible support comprises at least one of the elements selected from the group including PTFE or a support of biological origin, in particular a calcium-based, in particular a calcium carbonate-based, support of biological origin, preferably coral.

56. Kit according to Claim 54 or 55, characterized in that the constituent capable of inducing and/or promoting the gelation of the cells is collagen, in particular type I collagen, preferably at a concentration of the order of 1.5 mg/ml.

57. Kit according to Claim 54, characterized in that it contains a DNA comprising a sequence coding for the substance expressed and secreted by said cells.

58. Kit according to Claim 57, characterized in that it contains a retroviral vector according to any one of the Claims 32 to 42.

59. Kit according to any one of the Claims 54 to 58, characterized in that it contains cells having the capacity to express and secrete

naturally or after recombination a defined substance for example a substance having a therapeutic value.

60. Kit according to Claim 59, characterized in that the cells are recombinant cells according to anyone of the Claims 43 to 47.

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